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EXAMINER	
NOGUEROLA, ALEXANDER STEPHAN	
ART UNIT	PAPER NUMBER
1753	

DATE MAILED: 09/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,089	GRATZL ET AL.	
	Examiner	Art Unit	
	ALEX NOGUEROLA	1753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-9,13-19,21-27,29 and 30* is/are rejected.

7)☒ Claim(s) *5,6,10-12,20 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Danek et al. ("Voltammetric Studies on Kinetics of Uptake and Efflux at Catecholamine Transporters," Methods in Enzymology, vol. 296, pp. 649-660) ("Danek") in view of Earles et al. ("Rotating Disk Electrode Voltammetric Measurements of Dopamine Transporter Activity: An Analytical Evaluation," Analytical Biochemistry 264, 191-198 (1998)) ("Earles"). Note that the examiner does not known the month this article was published only the year, 1998, so for the purposes of the is rejection it is assumed that the article was published less one year prior to Applicants' earliest priority date of May 28, 1999.

Danek discloses a method of measuring efflux of a chemical from a cell or a population of cells (title; first paragraph of the Introduction; and third full sentence on page 650), the method including introducing the chemical to the cell and measuring an

electrochemical property of a medium surrounding the cell with an electrochemical system which includes a working electrode and a reference electrode, the property being related to a concentration of the chemical in the medium (Figure 1 and the first paragraph of Methods – *Apparatus*, which begins on page 650), the method characterized by

adding oxygen to the medium (fourth full sentence on page 651 and bottom of page 653). Although Danek does not mention that the oxygen is to increase a signal strength of the electrochemical property this is inherent because the 95% O_2/5% CO_2 stream is clearly provided to maintain the cells in a viable state. See, for example, the abstract and *Saturation of Oxygen in the Incubation Chamber* on page 196 of Earles, who also teaches directing a stream of 95% O_2/5% CO_2 across a solution in which dopamine efflux is to be electrochemically measured. If this oxygen stream was not provided some cells would likely die or deteriorate, thus lowering the signal strength.

5. Claims 1-4 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yi et al. ("Continuous in Situ Electrochemical Monitoring of Doxorubicin Efflux from Sensitive and Drug-Resistant Cancer Cells," Biophysical Journal, volume 75, November 1998, 2255-2261) ("Yi") in view of Earles et al. ("Rotating Disk Electrode Voltammetric Measurements of Dopamine Transporter Activity: An Analytical Evaluation," Analytical

Biochemistry 264, 191-198 (1998)) ("Earles") and the CAPLUS abstract for "Growth behavior of Chinese hamster ovary cells in a compact loop bioreactor: 1. Effects of physical and chemical environments," Journal of Biotechnology (1990), 15, 101-11) ("Kurano"). Note that Yi is by "another" because the instant application lists several inventors who are not listed as coauthors of the Yi article.

Addressing claim 1, Yi discloses a method of measuring efflux of a chemical from a cell or a population of cells (title and abstract), the method including introducing the chemical to the cell and measuring an electrochemical property of a medium surrounding the cell with an electrochemical system which includes a working electrode and a reference electrode, the property being related to a concentration of the chemical in the medium (abstract and Figure 1).

Yi does not mention adding oxygen to the medium to increase a signal strength of the electrochemical property.

Earles discloses a method of measuring efflux of a chemical from a cell or a population of cells (abstract), the method including measuring an electrochemical property of a medium surrounding the cell with an electrochemical system which includes a working electrode and a reference electrode, the property being related to a concentration of the chemical in the medium (abstract and Figure 1). Earles further teaches adding oxygen to the medium (*Saturation of Oxygen in the Incubation Chamber* on page 196 of Earles). It would have been obvious to one with ordinary skill in the art at the time of the invention to add oxygen as taught by Earles in the invention of Yi because as taught by Earles the oxygen will keep the cells or tissues viable (Chinese

hamster ovary cells also consume oxygen as shown by the Kurano abstract). Although Yi as modified by Earles does not mention that the oxygen is to increase a signal strength of the electrochemical property this is inherent because if this oxygen was not provided some cells would likely die or deteriorate, thus lowering the signal strength.

Addressing claim 2, for the additional limitation of this claim see in Yi the second column on page 2258 and the first paragraph in Discussion.

Addressing claim 3, for the additional limitation of this claim see in Yi the second paragraph of Measurement of doxorubicin concentrations close to the cell monolayer on page 2257.

Addressing claim 4, for the additional limitation of this claim note that Yi states, "Further development of this technique can lead to virtually continuous monitoring of drug efflux from a few cells or even a single cancer cells ..." and "This infers that it may be feasible to detect drug efflux from a single cancer cell with the techniques proposed in this work." See, respectively, the third full paragraph in the first column on page 2256 and fourth full paragraph on page 2260. Additionally, Yi discloses that monitoring of as few as four cells is possible. See the third full paragraph in the first column on page 2260. Thus, barring a contrary showing, using the method of Yi as modified by Earles and Kurano to monitor only one cell is just an obvious variant of monitoring a few cells.

Addressing claim 15, for the additional limitations of this claim see Measurement of doxorubicin concentrations close to the cell monolayer on page 2257 and Figure 3.

6. Claims 16, 22, 24, 25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yi et al. ("Continuous in Situ Electrochemical Monitoring of Doxorubicin Efflux from Sensitive and Drug-Resistant Cancer Cells," Biophysical Journal, volume 75, November 1998, 2255-2261) ("Yi") in view of Belmont et al. (US 6,900,043 B1) ("Belmont").

Addressing claim 16, Yi discloses an apparatus for measuring efflux of a chemical from a biological cell, or a population of cells (abstract), the apparatus including

a substrate (glass cover slip) having a surface which receives the cell (Figure 1A);

a medium on the substrate (Figure 1B);

an electrochemical monitoring system which measures an electrochemical property of the medium surrounding the cell, the property being related to a concentration of the chemical in the medium (abstract and Figure 1).

Yi does not mention a surface of the substrate having at least one attachment region to which the cell or population of cells attaches, the region being surrounded by a resistant region which resists attachment of cells. Belmont teaches encircling cells on a substrate with a hydrophobic pen. See col. 43:42-57. It would have been obvious to one with ordinary skill in the art at the time of the invention to create a hydrophobic region on the substrate which resists attachment of cells as taught by Belmont in the invention of Yi because this will prevent the cells from falling off or moving off the slide.

Addressing claim 22, for the additional limitation of this claim note the separated cells in Figure 1 of Yi.

Addressing claim 24, Yi does not mention having the surface include "a plurality of attachment regions which each attracts a single cell or group of cells, each attachment region having an associated working electrode positioned adjacent the attachment region." However, barring evidence to the contrary, such as unexpected results, this is just multiplication of parts for a multiplied effect. By just increasing the surface area of the surface a plurality of cells or groups of cells can be attached to the surface. This would allow, along with the plurality of working electrodes, simultaneous measurements to made on different cells at the same time. Such measurements may simply be redundancy for statistical purposes.

Addressing claim 25, for the additional limitation of this claim see Figure 1A of Yi.

Addressing claim 27, Yi discloses a method of measuring efflux of a chemical from a biological cell (abstract), or a population of cells (abstract), the method including introducing the chemical to the cell and measuring a property of a medium surrounding the cell or population of cells (abstract and Figures 1 and 4), the property being related to a concentration of the chemical in the medium (abstract and Figure 4), the method characterized by

positioning the cell or population of cells on a surface of a substrate by attachment of the cell or cell population to a region of the substrate which permits attachment (Figure 1).

Yi does not mention having the attractive region of the substrate being surrounded by a region which resists attachment of cells.

Belmont teaches encircling cells on a substrate with a hydrophobic pen. See col. 43:42-57. It would have been obvious to one with ordinary skill in the art at the time of the invention to create a hydrophobic region on the substrate which resists attachment of cells as taught by Belmont in the invention of Yi because this will prevent the cells from falling off or moving off the slide.

7. Claims 17-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yi et al. ("Continuous in Situ Electrochemical Monitoring of Doxorubicin Efflux from Sensitive and Drug-Resistant Cancer Cells," Biophysical Journal, volume 75, November 1998, 2255-2261) ("Yi") in view of Belmont et al. (US 6,900,043 B1) ("Belmont") as applied to claims 16 and 22 above, and further in view of Earles et al. ("Rotating Disk Electrode Voltammetric Measurements of Dopamine Transporter Activity: An Analytical Evaluation," Analytical Biochemistry 264, 191-198 (1998)) ("Earles") and the CAPLUS abstract for "Growth behavior of Chinese hamster ovary cells in a compact loop bioreactor: 1. Effects of physical and chemical environments," Journal of Biotechnology (1990), 15, 101-11) ("Kurano").

Addressing claim 17, Yi does not mention a source of oxygen containing gas which supplies oxygen to the medium to increase a signal strength of the electrochemical property.

Earles discloses a method of measuring efflux of a chemical from a cell or a population of cells (abstract), the method including measuring an electrochemical property of a medium surrounding the cell with an electrochemical system which includes a working electrode and a reference electrode, the property being related to a concentration of the chemical in the medium (abstract and Figure 1). Earles further teaches adding oxygen to the medium (*Saturation of Oxygen in the Incubation Chamber* on page 196 of Earles). It would have been obvious to one with ordinary skill in the art at the time of the invention to add oxygen as taught by Earles in the invention of Yi (and

thus provide a source of oxygen containing gas) because as taught by Earles the oxygen will keep the cells or tissues viable (Chinese hamster ovary cells also consume oxygen as shown by the Kurano abstract). Although Yi as modified by Earles does not mention that the oxygen is to increase a signal strength of the electrochemical property this is inherent because if this oxygen was not provided some cells would likely die or deteriorate, thus lowering the signal strength.

Addressing claim 18, that the source of oxygen containing gas comprises a container of substantially pure oxygen under pressure is implied because the oxygen is a stream of 95%O_2 – 5% CO_2. See *Saturation of Oxygen in the Incubation Chamber* on page 196 of Earles.

Addressing claim 19, for the additional limitation of his claim see Figure 1 in Yi.

Addressing claim 21, note that Yi states, "Further development of this technique can lead to virtually continuous monitoring of drug efflux from a few cells or even a single cancer cells ..." and "This infers that it may be feasible to detect drug efflux from a single cancer cell with the techniques proposed in this work." See, respectively, the third full paragraph in the first column on page 2256 and fourth full paragraph on page 2260. Additionally, Yi discloses that monitoring of as few as four cells is possible. See the third full paragraph in the first column on page 2260. Thus, barring a contrary

showing, having the resistant (hydrophilic) region of Yi as modified by Earles and Kurano sized for attachment of only one cell is just an obvious variant of monitoring a few cells.

8. Claims 7-9, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yi et al. ("Continuous in Situ Electrochemical Monitoring of Doxorubicin Efflux from Sensitive and Drug-Resistant Cancer Cells," Biophysical Journal, volume 75, November 1998, 2255-2261) ("Yi") in view of Earles et al. ("Rotating Disk Electrode Voltammetric Measurements of Dopamine Transporter Activity: An Analytical Evaluation," Analytical Biochemistry 264, 191-198 (1998)) ("Earles") and the CAPLUS abstract for "Growth behavior of Chinese hamster ovary cells in a compact loop bioreactor: 1. Effects of physical and chemical environments," Journal of Biotechnology (1990), 15, 101-11) ("Kurano") as applied to claims 1-4, 15 above, and further in view of Belmont et al.
(US 6,900,043 B1) ("Belmont").

Addressing claim 7, Yi as modified by Earles and Kurano does not mention a surface of the substrate having at least one hydrophilic region to which at [sic] the cell or the population of cells attaches, the hydrophilic region being surrounded by a

encircling cells on a glass slide with a hydrophobic pen. See col. 43:42-57. It would have been obvious to one with ordinary skill in the art at the time of the invention to create a hydrophobic region on the glass slide which resists attachment of cells as taught by Belmont in the invention of Yi as modified by Earles and Kurano because this will prevent the cells from falling off or moving off the slide.

Addressing claim 8, for the additional limitation of this claim note that Yi states, "Further development of this technique can lead to virtually continuous monitoring of drug efflux from a few cells or even a single cancer cells ..." and "This infers that it may be feasible to detect drug efflux from a single cancer cell with the techniques proposed in this work." See, respectively, the third full paragraph in the first column on page 2256 and fourth full paragraph on page 2260. Additionally, Yi discloses that monitoring of as few as four cells is possible. See the third full paragraph in the first column on page 2260. Thus, barring a contrary showing, using the method of Yi as modified by Earles and Kurano to monitor only one cell is just an obvious variant of monitoring a few cells.

Addressing claim 9, for the additional limitation of this claim note the separated cells in Figure 1 of Yi.

Addressing claim 13, for the additional limitation of this claim see the abstract and the first paragraph of the *Introduction* on page 2255.

Addressing claim 14, for the additional limitation of this claim see Measurement of doxorubicin concentrations close to the cell monolayer on page 2257.

9. Claims 16, 23, 25, 26, 27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parce et al. (US 5,496,697) ("Parce") in view of Belmont et al. (US 6,900,043 B1) ("Belmont").

Addressing claim 16, Parce discloses an apparatus for measuring efflux of a chemical from a biological cell, or a population of cells (abstract), the apparatus including

a substrate (2) having a surface which receives the cell (Figure 1);

a medium on the substrate (abstract);

an electrochemical monitoring system which measures an electrochemical property of the medium surrounding the cell, the property being related to a concentration of the chemical in the medium (col. 6:64 – col. 7:03).

Parce does not mention a surface of the substrate having at least one attachment region to which the cell or population of cells attaches, the region being surrounded by a resistant region which resists attachment of cells. Belmont teaches

encircling cells on a substrate with a hydrophobic pen. See col. 43:42-57. It would have been obvious to one with ordinary skill in the art at the time of the invention to create a hydrophobic region on the substrate which resists attachment of cells as taught by Belmont in the invention of Parce because this will prevent the cells from falling off or moving off the slide.

Addressing claim 23, for the additional limitation of this claim see in Parce col. 8:5-27.

Addressing claim 25, for the additional limitation of this claim see in Parce Figure 1.

Addressing claim 26, for the additional limitation of this claim see in Parce col. 9:48-64.

Addressing claim 27, Parce discloses a method of measuring efflux of a chemical from a biological cell (abstract), or a population of cells (abstract), the method including introducing the chemical to the cell and measuring a property of a medium surrounding the cell or population of cells (abstract and Figures 1-4), the property being related to a concentration of the chemical in the medium (abstract and col. 20:48 – col. 21:05), the method characterized by

positioning the cell or population of cells on a surface of a substrate by attachment of the cell or cell population to a region of the substrate which permits attachment (Figures 1-4 and col. 07:44 – col. 8:05).

Parce does not mention having the attractive region of the substrate being surrounded by a region which resists attachment of cells.

Belmont teaches encircling cells on a substrate with a hydrophobic pen. See col. 43:42-57. It would have been obvious to one with ordinary skill in the art at the time of the invention to create a hydrophobic region on the substrate which resists attachment of cells as taught by Belmont in the invention of Parce because this will prevent the cells from falling off or moving off the slide.

Addressing claim 29, Parce discloses a method of measuring transport of a chemical across a membrane of a human or other biological cell (abstract), the method comprising exposing the cell to chemical and measuring a property of a liquid medium disposed outside the cell (abstract), the property being related to a concentration of the chemical in the medium (abstract and col. 20:48 – col. 21:05), the method characterized by

providing a substrate surface with a region formed from a material to which the cell attaches (Figures 1-4 and col. 07:44 – col. 8:05)

patterning the substrate using photolithographic techniques to define at least one sensor adjacent the attachment region for sensing the property of the liquid medium (col. 09:65 – col. 10:14);

depositing the cell on the region (col. 09:15-17; col. 14:33-39; col. 15:04-09) and

after the step of exposing the cell to the chemical, detecting the property of the liquid medium surrounding the cell and determining the concentration of the chemical in the medium therefrom (abstract and col. 20:48 – col. 21:05).

Parce does not mention having the region to which the cells attach being surrounded by a region which resists attachment of cells.

Belmont teaches encircling cells on a substrate with a hydrophobic pen. See col. 43:42-57. It would have been obvious to one with ordinary skill in the art at the time of the invention to create a hydrophobic region on the substrate which resists attachment of cells as taught by Belmont in the invention of Parce because this will prevent the cells from falling off or moving off the slide.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claim 30 is rejected under 35 U.S.C. 102(e) as being anticipated by Farb et al. (US 6,048,722) ("Farb").

Farb discloses a method of measuring transport of a chemical across a membrane of a biological cell, the method comprising exposing the cell to the chemical (abstract);

depositing the cell on a the site (note cell 32 in Figures 3 and 20);

moving a sensor through a wall of the cell to contact the material in the cell (col. 7:39-65, col. 8:53-60, col. 09:28-45, and col. 17:29-40);

measuring a property of a material within the cell with the sensor, the property being related to a concentration of the chemical in the cell and determining the concentration of the chemical in the cell therefrom (col. 13:34–38, col. 13:53-62, col. 18:46 – col. 19:36, and claim 1).

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 21, 27, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a) Claim 21 recites the limitation "hydrophilic region" in line 3. There is insufficient antecedent basis for this limitation in the claim;

b) Claim 27 recites the limitation "the attractive region" in lines 10-11. There is insufficient antecedent basis for this limitation in the claim; and

c) Claim 30 recites the limitation "the material" in lines 8-9. There is insufficient antecedent basis for this limitation in the claim.

Claim Objections

14. Claims 1 and 7 are objected to because of the following informalities:

a) Claim 1, line 2 "cell," should be replaced with -- cell -- and "cells" with -- cells, --

b) Claim 7, line 6: "at" should be deleted.

Appropriate correction is required.

International Search Report for International Application No. PCT/US00/14805 ("Search Report")

15. US 5,496,697 was cited as an 'X" reference against claim 16 and as a "Y" reference against claims 27, 29, and 30 in the Search Report. US 4,901,446 A was cited as a "Y" reference against claim 30, apparently in combination with US 5,496,697. DE 19744649 A, for which US 6,379,916 B1 is an English language equivalent, was cited as a "Y" reference against claims 27 and 29 in the Search Report. US 5,496,697 is used to reject claims 16, 23, 25, 26, 29 in this Office action. Claim 30 requires the step of "moving a sensor through a wall of the cell to contact the material in the cell." In

contrast, In US 5,496,697 the sensors are photolithographically formed on the substrate surface. See col. 09:65 – col. 10:14. US 6,379,916 B1 mentions moving a sensor through the wall of a cell in passing, but this is for determining the conductivity in individual membrane sections, not for measuring a property of a material within the cell as claimed. See col. 1:14-37.

Allowable Subject Matter

16. Claims 5, 6, 10-12, 20, and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. The following is a statement of reasons for the indication of allowable subject matter:

a) Claim 5: the combination of limitations requires "the step of adding oxygen to the medium including bubbling an oxygen-containing gas into the medium." Danek as modified by Earles and Yi as modified by Earles and Kurano teach away from this limitations because Earles states, "Bubbling the 95% O_2 – 5% CO_2 directly into the solution during an experiment is not recommended because it is likely to result in bubbles on the electrode surface which interfere with the detection of the compound under study." See the last sentence in the second column on page 196, bridging to page 197.

b) Claim 6 depends from allowable claim 5.

c) Claim 10: the combination of limitations requires the working electrode to a carbon ring electrode, formed on the surface of the substrate. In Yi as modified by Earles and Kurano the working electrode is a linear carbon fiber "placed horizontally just on top of the monolayer of the cells." See Figure 1; first sentence of *Apparatus for electrochemical detection of doxorubicin* on page 2257 and third sentence form the end of *Measurement of doxorubicin concentrations close to the cell monolayer* on page 2257.

d) Claim 11: the combination of limitations requires "the step of introducing the chemical to the cell including injecting the chemical into the cell."

In Yi as modified by Earles and Kurano the chemical is introduced into the cell by incubating the cells with the chemical. See the second paragraph of *Measurement of doxorubicin concentrations close to the cell monolayer* on page 2257.

e) Claim 12 depends from allowable claim 11.

f) Claim 15: the combination of limitations requires the step of "preconcentrating effluxed chemical on the working electrode." This amplifies "the signal that might otherwise be too small to detect, due to typically low concentrations encountered in single cell efflux experiments." See page 17, lines 24-26 of the specification.

g) Claim 20: the combination of limitations requires the working electrode to a carbon ring electrode defining an annulus which surrounds the at least one attachment region. In Yi as modified by Belmont, Earles, and Kurano the working electrode is a linear carbon fiber "placed horizontally just on top of the monolayer of the cells." See Figure 1; first sentence of *Apparatus for electrochemical detection of doxorubicin* on page 2257 and third sentence form the end of *Measurement of doxorubicin concentrations close to the cell monolayer* on page 2257.

h) Claim 28: the combination of limitations requires the step of measuring the property to include employing a working electrode including a carbon ring electrode formed on the substrate adjacent the attractive region of the substrate.

In Yi as modified by Earles and Kurano the working electrode is a linear carbon fiber "placed horizontally just on top of the monolayer of the cells." See Figure 1; first sentence of *Apparatus for electrochemical detection of doxorubicin* on page 2257 and third sentence form the end of *Measurement of doxorubicin concentrations close to the cell monolayer* on page 2257. In Parce as modified by Belmont the working electrode silicon semiconductor electrode. See col. 5:1-9.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEX NOGUEROLA whose telephone number is (571) 272-1343. The examiner can normally be reached on M-F 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NAM NGUYEN can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alex Noguerola
Primary Examiner
AU 1753
September 5, 2006